APPENDIX 1

IN THE SPECIFICATION

The paragraph on page 1, lines 4-15 has been amended as follows:

This application is a **divisional of U.S. Serial No. 09/178,115 (filed October 23, 1998), which will issue as U.S. Patent No. 6,297,041 on October 2, 2001, which is a** continuation-in-part of ~~now pending~~ U.S. Serial No. 08/787,739~~,~~ (filed January 24, 1997), **which issued as U.S. Patent No. 6,027,887 on February 22, 2000,** which in turn is a continuation-in-part of the following seven ~~pending~~ U.S. Serial Nos., all of which were filed on June 7, 1995: **U.S. Serial No.** 08/485,049, **which issued as U.S. Patent 6,204,370 on March 20, 2001**, **U.S. Serial No.** 08/486,756, **which issued as U.S. Patent 5,981,711 on November 9, 1999**, **U.S. Serial No.** 08/477,504, **which issued as U.S. Patent No. 5,972,353 on October 26, 1999**, **U.S. Serial No.** 08/481,658, **which issued as U.S. Patent No. 5,955,075 on September 21, 1999**, **U.S. Serial No.** 08/485,862, **which issued as U.S. Patent No. 5,989,838 on November 23, 1999**, **U.S. Serial No.** 08/485,863, **which issued as U.S. Patent No. 6,093,858 on July 25, 2000** and **U.S. Serial No.** 08/487,077, **issued as U.S. Patent No. 6,069,242 on May 30, 2000**. Those seven applications are continuations-in-parts of now pending U.S.

Serial No. 08/260,190 (filed June 15, 1994), which, in turn, is a continuation-in-part of ~~now pending~~ U.S. Serial No. 08/177,093 (filed December 30, 1993), **which issued as U.S. Patent No. 6,051,226 on April 18, 2000,** which is in turn a continuation-in-part of U.S. Serial No. 07/964,589 (filed October 21, 1992), which ~~was~~ issued as U.S. Patent No. 5,387,676 on February 7, 1995. This application declares priority under 35 USC § 120 from those U.S. applications and patent**s**, and also under 35 USC § 119 from the now ~~pending~~ **abandoned** Czechoslovakian patent application PV-709-92 (filed March 11, 1992).

The paragraph on page 3, lines 12-25 has been amended as follows:

MN/CA IX has a number of properties that distinguish it from other known CA isoenzymes and evince its relevance to oncogenesis. Those properties include its density dependent expression in cell culture, (e.g., HeLa cells), its correlation with the tumorigenic phenotype of somatic cell hybrids between HeLa and normal human fibroblasts, its close association with several human carcinomas and its absence from corresponding normal tissues [e.g., Zavada et al., Int. J. Cancer, 54: 268-274 ~~(1933)~~ **(1993)**; Pastorekova et al., Virology, 187: 620-626 (1992); Liao et al., Am. J. Pathol., 145: 598-609 (1994);

Pastorek et al., Oncogene, 9: 2788-2888 (1994); Cote, Women's Health Weekly: News Section, p. 7 (March 30, 1998); Liao et al., Cancer Res., 57: 2827 (1997); Vermylen et al., "Expression of the MN antigen as a biomarker of lung carcinoma and associated precancerous conditions," Proceedings AACR, 39: 334 (1998); McKiernan et al., Cancer Res., 57: 2362 (1997); and Turner et al., Hum. Pathol., 28(6): 740 (1997)]. In addition, ~~the~~ **the** *in vitro* transformation potential of MN/CA IX cDNA has been demonstrated in NIH 3T3 fibroblasts [Pastorek et al., id.].

The paragraph on page 11, lines 23-26 has been amended as follows:

Identified herein is the location of the MN protein binding site. Also identified are MN oligopeptides that compete for attachment to cells with immobilized MN protein. Such oligopeptides prevent cell-cell adhesion and the formation of ~~intracellular~~ **intercellular** contacts.

The paragraph on page 14, lines 22-30 has been amended as follows:

A hybridoma that produces a representative MN-specific antibody, the monoclonal antibody M75 (Mab M75), was deposited at the ~~under ATCC~~ **ATCC under** Number HB 11128 as indicated above.

The M75 antibody was used to discover and identify the MN protein and can be used to identify readily MN antigen in Western blots, in radioimmunoassays and immunohistochemically, for example, in tissue samples that are fresh, frozen, or formalin-, alcohol-, acetone- or otherwise fixed and/or paraffin-embedded and deparaffinized. Another representative MN-specific antibody, Mab MN12, is secreted by the hybridoma MN 12.2.2, which was deposited at the ATCC under the designation HB 11647.

Line 25 on page 17 has been amended as follows:

IPTG - isopropyl-~~Beta~~ **beta**-D-thiogalacto-pyranoside

The paragraph on page 31, lines 7-13 has been amended as follows:

In Zavada et al., id., the isolation of a partial MN cDNA clone of 1397 bp in length was described. A lambda gt11 cDNA library of LMCV-infected HeLa cells was prepared and subjected to immunoscreening with Mab M75 in combination with goat anti-mouse antibodies conjugated with alkaline phosphatase. One positive clone was picked and subcloned into the NotI site of ~~pBluscript~~ **pBluescript** KS [~~Stratagen~~ **Stratagene**; La Jolla, CA (USA)] thereby creating ~~pBluscript-MN~~ **pBluescript-MN**.

TABLE 1 on page 34, lines 1-33 has been amended as follows:

TABLE 1

Exon-Intron Structure of the Human MN Gene

~~Intron~~ **Exon**	Size	Genomic Position**	SEQ ID NO	5'splice acceptor	SEQ ID NO
1	445	*3507-3951	28	AGAAG gtaagt	67
2	30	5126-5155	29	TGGAG gtgaga	68
3	171	5349-5519	30	CAGTC gtgagg	69
4	143	5651-5793	31	CCGAG gtgagc	70
5	93	5883-5975	32	TGGAG gtacca	71
6	67	7376-7442	33	GGAAG gtcagt	72
7	158	8777-8934	34	AGCAG gtgggc	73
8	145	9447-9591	35	GCCAG gtacag	74
9	27	9706-9732	36	TGCTG gtgagt	75
10	82	10350-70431	37	CACAG gtatta	76
11	191	10562-10752	38	ATAAT end	

Intron	Size	Genomic Position **	SEQ ID NO	3'splice acceptor	SEQ ID NO
1	1174	3952-5125	39	atacag GGGAT	77
2	193	5156-5348	40	ccccag GCGAC	78
3	131	5520-5650	41	acgcag TGCAA	79
4	89	5794-5882	42	tttcag ATCCA	80
5	1400	5976-7375	43	ccccag GAGGG	81
6	1334	7443-8776	44	tcacag GCTCA	82
7	512	8935-9446	45	ccctag CTCCA	83
8	114	9592-9705	46	ctccag TCCAG	84
9	617	9733-10349	47	tcgcag GTGACA	85
10	130	10432-10561	48	acacag AAGGG	86

** positions are related to nt numbering in whole genomic sequence including the 5' flanking region [Figure 2A-F]

* number corresponds to transcription initiation site determined below by ~~Rnase~~ **RNase** protection assay

Line 26 on page 45 has been amended as follows:

EMSA Supershift ~~analysis~~ **Analysis**

The paragraph on page 71, lines 27-32 has been amended as follows:

MAb M75. Monoclonal antibody M75 (MAb M75) is produced by mouse lymphocytic hybridoma VU-M75, which was initially deposited in the Collection of Hybridomas at the Institute of Virology, Slovak Academy of Sciences (Bratislava, ~~Czechoslovakia~~ **Slovakia**) and was deposited under ATCC Designation HB 11128 on September 17, 1992 at the American Type Culture Collection (ATCC). The production of hybridoma VU-M75 is described in Zavada et al., WO 93/18152.

The paragraph on page 78, lines 13-18 has been amended as follows:

The M75 MAb (or, for example, as a single chain antibody, or as its variable region) is exemplary of such a MN-specific antibody. Example 5 discloses heptapeptides (SEQ ID NOS: 107-109) that bind to the enzymatic center of the CA domain of the MN protein and, selected peptides or proteins comprising such heptapeptides would also be expected to bind to a binding ~~side~~ **site** on the extracellular domain of the MN protein.

The paragraph on page 81, lines 7-15 has been amended as follows:

MN proteins and/or polypeptides may be synthesized or prepared recombinantly or otherwise biologically, to comprise one or more amino acid sequences corresponding to one or more epitopes of the MN proteins either in monomeric or multimeric form. Those proteins and/or polypeptides may then be incorporated into vaccines capable of inducing protective immunity. Techniques for enhancing the antigenicity of such polypeptides include incorporation into a multimeric structure, binding to a highly immunogenic protein carrier, for example, keyhole limpet hemocyanin (KLH), or ~~diptheria~~ **diphtheria** toxoid, and administration in combination with adjuvants or any other enhancers of immune response.

The paragraph on page 98, lines 24-30 has been amended as follows:

The MN protein is a candidate for being the product of the critical oncogene; its expression in the hybrids has been shown to correlate with their tumorigenicity [e.g., Zavada et al. (1993), supra]. The present results indicate that additional mechanisms might exist, which are able to "heal" a ~~carcerous~~ **cancerous** cell. Understanding the molecular mechanisms of action

of MN protein in normal and in tumor cells and elucidating how the reversion works may provide new approaches to cancer therapy.

IN THE CLAIMS

Claim 22 has been amended as follows:

22. (Amended) An anti-idiotype antibody to ~~a MN-specific~~ **an** antibody **which specifically binds to an MN protein, wherein said Mn protein is encoded by a nucleic acid selected from the group consisting of:**

(a) SEQ ID NO: 1;

(b) polynucleotides that hybridize under stringent conditions to SEQ ID NO: 1's complement; and

(c) polynucleotides that differ from SEQ ID NO: 1 or from the polynucleotide sequences of (b) due to the degeneracy of the genetic code.

Claim 23 has been amended as follows:

23. (Amended) An anti-idiotype antibody according to Claim 22, wherein said ~~MN-specific~~ antibody **that is specific for said MN protein,** is either the M75 monoclonal antibody secreted from the hybridoma VU-M75, which was deposited at the American Type Culture Collection under ATCC No. HB 11128, or the MN12 monoclonal antibody that is secreted from the hybridoma MN

12.2.2, which was deposited at the American Type Culture Collection under ATCC No. HB 11647.

APPENDIX 2

22. (Amended) An anti-idiotype antibody to an antibody which specifically binds to an MN protein, wherein said MN protein is encoded by a nucleic acid selected from the group consisting of:

(a) SEQ ID NO: 1;

(b) polynucleotides that hybridize under stringent conditions to SEQ ID NO: 1's complement; and

(c) polynucleotides that differ from SEQ ID NO: 1 or from the polynucleotide sequences of (b) due to the degeneracy of the genetic code.

23. (Amended) An anti-idiotype antibody according to Claim 22, wherein said antibody that is specific for said MN protein, is either the M75 monoclonal antibody secreted from the hybridoma VU-M75, which was deposited at the American Type Culture Collection under ATCC No. HB 11128, or the MN12 monoclonal antibody that is secreted from the hybridoma MN 12.2.2, which was deposited at the American Type Culture Collection under ATCC No. HB 11647.

24. An anti-anti-idiotype antibody to the anti-idiotype antibody according to Claim 22.

25. An anti-anti-idiotype antibody to the anti-idiotype antibody according to Claim 23.

26. An anti-anti-idiotype antibody according to Claim 24 which is polyclonal.

27. An anti-anti-idiotype antibody according to Claim 25 which is polyclonal.

30. An anti-idiotype antibody to an antibody which specifically binds to an MN polypeptide, wherein said MN polypeptide is encoded by a nucleic acid that comprises a polynucleotide containing at least 29 nucleotides, said nucleic acid being selected from the group consisting of:

(a) SEQ ID NO: 1;

(b) polynucleotides that hybridize under stringent conditions to SEQ ID NO: 1's complement; and

(c) polynucleotides that differ from SEQ ID NO: 1 or from the polynucleotide sequences of (b) due to the degeneracy of the genetic code.

31. The anti-idiotype antibody according to Claim 30, wherein said antibody that is specific to said MN polypeptide is either the M75 monoclonal antibody secreted from the hybridoma VU-M75, which was deposited at the American Type Culture Collection under ATCC No. HB 11128, or the MN12 monoclonal antibody that is secreted from the hybridoma MN 12.2.2, which was deposited at the American Type Culture Collection under ATCC No. HB 11647.

32. An anti-anti-idiotype antibody to the anti-idiotype antibody according to Claim 30.

33. An anti-anti-idiotype antibody to the anti-idiotype antibody according to Claim 31.

34. An anti-anti-idiotype antibody according to Claim 32 which is polyclonal.

35. An anti-anti-idiotype antibody according to Claim 33 which is polyclonal.

36. The anti-idiotype antibody according to Claim 30 wherein said nucleic acid comprises a polynucleotide containing at least 50 nucleotides.

37. The anti-idiotype antibody according to Claim 30 wherein said polynucleotide comprises at least 100 nucleotides.

38. The anti-idiotype antibody according to Claim 30 wherein said nucleic acid comprises a polynucleotide containing at least 150 nucleotides.

39. An anti-anti-idiotype antibody to the anti-idiotype antibody according to Claim 36.

40. An anti-anti-idiotype antibody to the anti-idiotype antibody according to Claim 37.

41. An anti-anti-idiotype antibody to the anti-idiotype antibody according to Claim 38.

42. An anti-idiotype antibody to an antibody which specifically binds to an MN polypeptide, wherein said MN polypeptide is encoded by a nucleic acid that comprises a

polynucleotide containing at least 25 nucleotides, said nucleic acid being selected from the group consisting of:

(a) SEQ ID NO: 1;

(b) polynucleotides that hybridize under stringent conditions to SEQ ID NO: 1's complement; and

(c) polynucleotides that differ from SEQ ID NO: 1 or from the polynucleotide sequences of (b) due to the degeneracy of the genetic code.

43. The anti-idiotype antibody according to Claim 42 wherein said nucleic acid comprises a polynucleotide containing at least 27 nucleotides.

44. An anti-anti-idiotype antibody to the anti-idiotype antibody according to Claim 42.

45. An anti-anti-idiotype antibody to the anti-idiotype antibody according to Claim 43.

46. The anti-idiotype antibody according to Claim 22 wherein said MN protein is encoded by SEQ ID NO: 1 or by a fragment of SEQ ID NO: 1.

47. The anti-idiotype antibody according to Claim 30 wherein said MN polypeptide is encoded by a fragment of SEQ ID NO: 1.

48. The anti-idiotype antibody according to Claim 42 wherein said MN polypeptide is encoded by a fragment of SEQ ID NO: 1.

49. An anti-anti-idiotype antibody to the anti-idiotype antibody according to Claim 46.

50. An anti-anti-idiotype antibody to the anti-idiotype antibody according to Claim 47.

51. An anti-anti-idiotype antibody to the anti-idiotype antibody according to Claim 48.

52. The anti-idiotype antibody according to Claim 22 wherein said stringent hybridization conditions comprise 50% formamide at 42 degrees C.